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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,467	03/26/2001	Laurent Coen	3495.0174-01	7062

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/18/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/816,467	Coen et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 24, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19 and 21-33* is/are pending in the application.

4a) Of the above, claim(s) *1-16 and 24-33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *17-19 and 21-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jun 29, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7, 9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of group IV, claims 17-19 and 21-23 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that a vector or a host cell comprising the vector, and a method of treatment using a protein or a vector do not require serious burden of examination, thus, groups IV-VII should be examined together. This is not found persuasive because peptides and nucleic acid or cells have different chemical structures, physical properties and biological functions, and have different classifications that require separate search. A method of treating a disease with a peptide, a method of treating a disease with a nucleic acid, and a method of delivering to a subject are different from each other. They differ at least in objectives, method steps, reagents and dosages used, schedules used, response variables, and criteria for success. Further, a peptide can be used to produce an antibody against said peptide other than the use in treating a disease.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-16 and 24-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Applicants' preliminary amendment filed 6-29-01 has been entered. Claim 20 has been canceled. Claims 8, 15, 16, 19, 21, 24, 25 and 29-31 have been amended. Claims 32 and 33 have been added. Claims 1-19 and 21-33 are pending and claims 17-19 and 21-23 are under consideration.

Priority

3. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims 17 and 18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 17 and 18 of copending Application No. 09/501,787. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 19 and 21-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19 and 21-23 of copending

Application No. 09/501,787. Although the conflicting claims are not identical, they are not patentably distinct from each other because, although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 19 and 21-23 of the present application are directed to a composition containing a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof, and an amino acid variant fragment of said hybrid fragment.

Claims 19 and 21-23 of the Application No. 09/501,787 are directed to a composition containing a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof, or further containing fragment A devoid of its zinc-binding motif and an amino acid variant fragment of said hybrid fragment. The scope of claims 19 and 21-23 of the Application No. 09/501,787 encompass the subject matter of claims 19 and 21-23 of the present application, thus, it would be obvious for one of ordinary skill at the time of the invention to practice the claimed invention of the present application according to the claimed invention of Application No. 09/501,787.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "or a fraction thereof of at least 11 amino acid residues " in lines 2-3 of claims 17 and 18 is vague and renders the claims indefinite. It is unclear whether the fraction is a fraction of only fragment B or a fraction of the combination of fragment C and fragment B. Claims 19 and 21-23 depend on claim 17 but fails to clarify the indefiniteness.

The phrase "a polynucleotide encoding a protein or a polypeptide with a promoter..., and optionally an enhancer" in claim 23 is vague and renders the claim indefinite. It is unclear what is intended to be claimed, a polynucleotide encoding a protein, a polypeptide with a promoter, or an enhancer, or a polynucleotide encoding a polypeptide and said polynucleotide has a promoter or an enhancer.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 reads on an amino acid variant fragment of a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof of at least 11 amino acid residues capable of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction.

The specification only discloses a hybrid fragment of LacZ + TTC (fragment C of tetanus toxin + 11 amino acid residues of fragment B). The claims encompass any amino acid variants that differs from the disclosed TTC via substitution, deletion or addition and includes various unknown and unidentified amino acid sequences having the activity of TTC.

The claim encompasses a genus of numerous structural variants of TTC having the activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of TTC or its variants for its activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction. There is no evidence of record that a particular region of amino acid residues within TTC is essential to its transferring activity. Structural features that could distinguish compounds in the genus from others in the protein or peptide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because

specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the amino acid sequence of TTC as disclosed in the present application is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed amino acid variant fragments. Thus, it is concluded that the written description requirement is not satisfied for the amino acid variant fragments as claimed.

12. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hybrid fragment of tetanus toxin, LacZ + TTC, as disclosed, does not reasonably provide enablement for any amino acid variant fragment having the same properties as said hybrid fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 19 reads on an amino acid variant fragment of a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof of at least 11 amino acid residues capable of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction.

The specification only discloses a hybrid fragment of LacZ + TTC (fragment C of tetanus toxin + 11 amino acid residues of fragment B). The claims encompass any amino acid variants that differs from the disclosed TTC via substitution, deletion or addition and includes various unknown and unidentified amino acid sequences having the activity of TTC.

The claim encompasses a genus of numerous structural variants of TTC having the activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of TTC or its variants for its activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction. There is no evidence of record that a particular region of amino acid residues within TTC is essential to its transferring activity.

The specification also fails to provide adequate guidance and evidence how and which amino acid residue within TTC fragment can be deleted or substituted, or what amino acid residue can be added to TTC fragment such that the resulting amino acid variant still retain the activity of TTC fragment as disclosed. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar or higher activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of

particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the lack of detailed information regarding the structural and functional requirements of the TTC fragment and its variants, and the unpredictability of polypeptide function from mere amino acid sequence, it would be unpredictable whether the amino acid variant fragment of TTC would have the activity of TTC fragment as disclosed. In view of such, one skilled in the art at the time of the invention would not know how to make and/or use the claimed amino acid variant fragment of the hybrid fragment of tetanus toxin.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and

the breadth of the claims that it would require a skilled artisan at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 FEBS Letters, Vol. 336, No. 1, p. 175-180.

Claims 17-19 and 21-23 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof of at least 11 amino acid residues, an amino acid

variant fragment of said hybrid fragment, a composition containing said hybrid fragment in association with an active molecule, and a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction thereof, and further containing fragment A devoid of its zinc-binding motif.

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo. The toxic portion of the protein resides in the amino terminal (e.g. p. 3 and 4).

Mueller does not teach a hybrid fragment comprising fragment C of tetanus toxin and at least 11 amino acid residues of fragment B or a hybrid fragment further comprises a fraction of a fragment A devoid of its toxic activity corresponding to zinc-binding motif between amino acid residues 225 and 245.

Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on calcium induced catecholamine release (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to generate claimed hybrid fragment or composition because C-fragment of the tetanus toxin alone is not toxic and the toxic portion of the protein resides in the amino terminal, and in combination with the teaching of Mueller that the putative zinc-binding domain constitutes the active site of

the tetanus toxin light chain would make it obvious for one of ordinary skill to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport. It also would have been obvious for one of ordinary skill at the time of the invention to include a portion of fragment B with fragment C of tetanus toxin because the toxic region of tetanus toxin resides in the putative zinc-binding domain, which is at amino terminal, and inclusion of a portion of non-toxic region of tetanus toxin would not contribute to the toxicity of tetanus toxin.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a non-toxic tetanus toxin fragment capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Hohne-Zell with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.